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Letters

Decreased Plasma Levels of Active Glucagon-Like Peptide-1 in Coronary Artery Disease

Glucagon-like peptide-1 (GLP-1) is an incretin hormone and has cardiovascular protective effects (1). Vascular cells express GLP-1 receptors, and studies have demonstrated that enhancing GLP-1 activity exhibits beneficial effects on atherosclerosis in animal models (2). However, the impact of endogenously secreted GLP-1 on coronary artery disease (CAD) has not been clinically examined. The aim of this study was to investigate the associations between plasma active GLP-1 (aGLP-1) levels, CAD, and coronary plaque complexity during fasting or during a 75 g oral glucose tolerance test (75g-OGTT).

We describe a cross-sectional observational study (Plasma Levels of Active Glucagon-Like Peptide-1 and Coronary Artery Disease; UMIN000008881) measuring plasma aGLP-1 levels (Glucagon-Like Peptide-1 [Active] enzyme-linked immunosorbent assay, Millipore Corporation, Massachusetts) from a peripheral vein during fasting or a 75g-OGTT in 236 stable CAD patients (68 ± 10 years of age, 68% male, 32% diabetes mellitus [DM]) who underwent coronary angiography at Kumamoto University Hospital between April 2009 and August 2011. These patients were compared with 97 non-CAD patients of similar age and sex distribution with a high-risk condition (DM, or more than 2 conventional coronary risk factors) during the same study period (DM: 16%). The 75g-OGTT was performed in all patients without overt DM. We assessed coronary plaque complexity using the SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) score in CAD patients.

Fasting active GLP-1 (F-aGLP-1) levels were not detectable (<2 pmol/l) in a higher percentage of CAD patients compared to non-CAD patients (n = 71, 30% vs. n = 10, 10%; $p < 0.001$). In patients whose fasting active GLP-1 levels were detectable, fasting GLP-1 levels were significantly lower in CAD patients (n = 165) than in non-CAD patients (n = 87) (3.2 [2.6 to 4.2] pmol/l vs. 3.8 [2.8 to 5.4] pmol/l; $p = 0.001$).

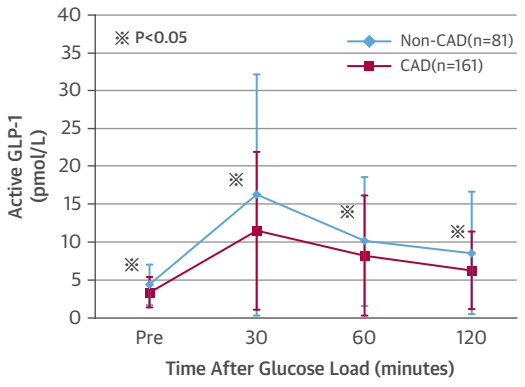
We divided all participants (n = 333) into tertiles of F-aGLP-1 levels (cutoff points: lowest, <2.3 pmol/l; middle, 2.3 to 3.5 pmol/l; highest, >3.5 pmol/l). The prevalence of CAD decreased across tertiles (lowest: n = 94, 85%; middle: n = 84, 73%; highest: n = 58, 54%; $p < 0.001$). Stepwise backward multivariate logistic regression analysis, including various classical risk factors (e.g., DM) demonstrated that F-aGLP-1 levels were independently associated with the presence of CAD (per tertile decrease; odds ratio [OR]: 2.44; 95% confidence interval [CI]: 1.73 to 3.45; $p < 0.001$) (c statistic without F-aGLP-1: 0.659; with F-aGLP-1: 0.753).

In 242 patients without overt DM (CAD: n = 161), F-aGLP-1 levels were still independently associated with the presence of CAD (per tertile decrease, OR: 2.16; 95% CI: 1.47 to 3.19; $p < 0.001$). The 75g-OGTT identified patients with newly diagnosed DM (n = 38, 16%), impaired glucose tolerance (n = 77, 32%), and normal glucose tolerance (NGT) (n = 127, 52%). Even in patients with NGT, F-aGLP-1 levels independently correlated with the presence of CAD (per tertile decrease, OR: 2.27; 95% CI: 1.32 to 3.89; $p = 0.003$).

Plasma glucose levels and insulin levels during 75g-OGTT were comparable between the 2 groups. However, levels of aGLP-1 during 75g-OGTT were significantly lower in CAD patients than in non-CAD patients (**Figure 1**). Using forced inclusion models with age, sex, the presence of hypertension, dyslipidemia, and metabolic syndrome in the multivariate logistic regression analysis, F-aGLP-1 and aGLP-1 at 60 min and 120 min during 75g-OGTT but not aGLP-1 at 30 min or peak aGLP-1 were independently associated with the presence of CAD in patients without overt DM (C statistic without aGLP-1: 0.684; with F-aGLP-1: 0.745; aGLP-1 at 30 min: 0.694; 60 min: 0.712; 120 min: 0.725; peak: 0.687). F-aGLP-1 had the best model fits, as assessed by Nagelkerke R^2.

Of the 236 CAD patients, 54 (23%) showed severe coronary plaque complexity (SYNTAX score ≥33). Multivariate logistic regression analysis demonstrated that F-aGLP-1 levels were independently associated with the presence of severe coronary plaque complexity (per tertile decrease, OR: 1.65; 95% CI:

FIGURE 1 Active GLP-1 Levels During 75g-OGTT in Non-Diabetes Mellitus Patients With or Without CAD



Values are calculated as the mean ± SD. CAD = coronary artery disease; GLP-1 = glucagon-like peptide-1; OGTT = oral glucose tolerance test.

1.08 to 2.54; p = 0.02) (C statistic without F-aGLP-1: 0.664; with F-aGLP-1: 0.705).

The present study is the first to demonstrate significantly reduced plasma aGLP-1 levels in a fasting state and during 75g-OGTT in CAD patients. Lower aGLP-1 levels were significantly correlated with the presence of CAD. Furthermore, lower F-aGLP-1 levels were associated with severe coronary plaque complexity in CAD patients. These results suggested that there may be a pathophysiological link between endogenous aGLP-1 and CAD.

Although previous reports have demonstrated that incretin-related drugs attenuated the development of atherosclerotic lesions in animal models (2), a large clinical study failed to demonstrate any benefit of dipeptidyl peptidase-4 inhibition on ischemic events in patients with established disease (3). Further studies are warranted to clarify clinical significance of GLP-1 in CAD.

In summary, plasma aGLP-1 levels were significantly reduced in CAD patients, and lower plasma aGLP-1 levels were independently correlated with the presence of CAD and coronary plaque complexity. The gut-derived endogenous aGLP-1 may have a significant association with human coronary atherosclerosis.

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Influence of Sex on Mortality and Perioperative Outcomes in Patients Undergoing TAVR

Insights From the FRANCE 2 Registry

Transcatheter aortic valve replacement (TAVR) is an alternative to surgery for high-risk or inoperable patients (1). However, few data, with varied and confusing follow-up timings, are available (2,3)